



T/GB 2003 / 0 0 3 5 7 5



INVESTOR IN PEOPLE

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ
WFO

12 FEB 2003
23 SEP 2003
PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

**CERTIFIED COPY OF
PRIORITY DOCUMENT**

Signed

Dated 2 September 2003

BEST AVAILABLE COPY

BEST AVAILABLE COPY

Patents Act 1977
(Rule 16)

Request for grant of a patent

(See the notes on the back of this form. You can also see an explanatory leaflet from the Patent Office to help you fill in this form.)



The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

Fee: £0

1. Your reference

44963/JMD/MAR

2. Patent application number

(The Patent Office will fill in this part)

0218916.5

114 AUG 2002

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Intercytex Limited
Incubator Building
Grafton Street
Manchester
M13 9XX

Patents ADP number (if you know it)

8072423001

If the applicant is a corporate body, give the country/state of incorporation

United Kingdom

4. Title of the invention

Kidney Formation

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number (if you know it)

91001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application
(if you know it)

Date of filing
(day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

See note (d))

YES

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document.

Continuation sheets of this form

Description	14	✓
Claim(s)	3	✓ W~
Abstract	0	
Drawing(s)	8 + 8	✓

10. If you are also filing any of the following, state how many against each item.

Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	0
Request for preliminary examination and search (Patents Form 9/77)	1
Request for substantive examination (Patents Form 10/77)	0
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature

Date

14 August 2002

Reddie + Gore

12. Name and daytime telephone number of person to contact in the United Kingdom

J M DAVIES
01223 360350

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or such direction has been revoked.

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered 'Yes' Patents Form 7/77 will need to be filed.
- Once you have filled in the form you must remember to sign and date it.
- For details of the fee and ways to pay please contact the Patent Office.

Kidney Formation

The present invention relates to sites for implantation of an embryonic kidney metanephros or kidney rudiment.

5

Kidneys are excretory organs that maintain chemical and physical constancy of blood and other body fluids by removing superfluous water and materials which are biologically useless or toxic. The kidney is comprised of a number of functional units called nephrons. Each nephron has a complex structure with two main parts: the glomerulus and the renal tubule. The glomerulus comprises non-anastomosing capillaries located in the cortical substance and is surrounded by the capsule of Bowman, which is part of the renal tubule. The renal tubule is located partly in the cortical substance and partly in the medullary substance and terminates into a collecting tubule which opens into a ureter. The ureter opens into the urinary bladder.

20

During embryogenesis, the rudiments of the permanent kidneys, the metanephroi, appear during the fifth week of gestation in humans, during day 12 of embryonic rat development and during day 11 of embryonic mouse development. Humans develop a full complement of nephrons by approximately 35 weeks of gestation. However, in rodents nephrogenesis continues for the first 2 weeks following birth, when nephrons continue to develop from a nephrogenic zone located at the periphery of the kidney. Once mammalian renal development is complete, no new nephrons are formed under any conditions.

30

Loss of kidney function resulting in end-stage renal failure is a major clinical problem with a wide variety of causes including diabetes, immune mediated inflammatory disease, hypertension, urinary tract infections and

35

genetic predisposition (polycystic kidney disease). In the UK, the cost of renal replacement therapy (RRT) consumes 2% (£1.2 Billion) of the NHS Budget with a predicted rise to 3% within 5 years. In the US, the annual cost is estimated to be in excess of \$15 billion.

During 1999 in the UK, approximately 5350 people started renal replacement therapy for the first time, joining 31,147 patients already receiving treatment. Without prompt suitable treatment, death is inevitable. Currently, 52% of patients receive dialysis treatment in hospital or at home using a haemodialysis machine or peritoneal dialysis, whereas 48% of patients receive a kidney transplant the majority from an unrelated donor. All dialysis methods have their specific problems and while these techniques are life sustaining, patients lead a poor quality of life and are at high risk of death from cardiovascular disease. While transplantation is regarded as a superior replacement method, at present it requires a major surgical procedure and lifelong immunosuppressive therapy with significant increased risk of death from serious infection and cancer.

The half-life of a kidney transplant is currently about 8 years, which means that young patients face the potential ordeal of 3 or 4 kidney transplants during their lifetime. However, transplantation is greatly limited by a severe shortage of donor organs, which is unlikely to change in the foreseeable future. Currently 5500 people in the UK are on the waiting list for kidney transplantation and yet only 1500 kidneys are available annually for transplantation. This organ shortage is replicated throughout the developed world. In the developing world, renal failure is often a death sentence as the current technology is unavailable or prohibitively expensive. Globally, the clinical need for the development of

alternative renal replacement therapies is enormous.

Use of embryonic kidneys to form chimeric kidneys is disclosed in USP 5,976,524 (Hammerman), which is
5 incorporated herein by reference in its entirety. Increased metanephron mass is achieved by transplantation of embryonic kidney metanephroi (E14 or E15 in rats) implanted next to the omentum or under the renal capsule.

10 Hammerman's approach involves transplanting embryonic day 15 metanephroi into the omentum of an adult host, the metanephroi are then left to develop for approximately 4 weeks before the metanephric ureter is connected to the adult ureter using an end-end anastomosis. At best, this
15 results in 5-7% renal function compared to normal. Using the Hammerman technique, development and vascularisation of new kidney structures is relatively slow (about 6 weeks) and an inflammatory response, which requires an immunosuppressive regime and/or anti-inflammatory
20 approach, is observed.

Current therapies for end stage renal failure such as dialysis offer 10%-15% renal function. It is thought that to produce an effective product, the renal function of
25 kidneys formed from transplanted metanephroi should be improved. There is therefore the need for a more effective method to produce kidneys from transplanted metanephroi.

According to the present invention, there is provided in a
30 first aspect a method of increasing the nephron mass of a mammalian recipient comprising implanting a metanephros of an embryonic mammalian donor on or near a large blood vessel of the recipient under conditions that allow the metanephros to become vascularised.

35

The method may allow for improved development (e.g. more

glomeruli), - improved vasculature and a reduced inflammatory/immune response compared with Hammerman's approach. This result could not have been expected from the prior art as the environment of embryonic development of metanephroi more closely resembles the Hammerman transplantation site than that of the present invention. A reduced inflammatory response may also be regarded as unexpected as a large blood vessel might be expected to increase the transport of inflammatory molecules to the site of transplantation.

In a preferred embodiment, the metanephros is implanted in the peritoneal cavity.

In a most preferred embodiment, the vascularised metanephros forms a chimeric kidney that produces urine and develops a ureter that facilitates externalisation of the urine.

The resulting chimeric kidney may be heavily vascularised and have improved development compared with implantation of metanephroi next to the omentum. In terms of gross morphology, the chimeric organs produced by the present method are shown in the Experimental section below to look like a kidney rather than "pink structures" often produced by transplantation next to the omentum. There appear to be differences also at the histological level. The chimeric organs produced by transplantation to the new site are shown in the Experimental section below to have more glomeruli, part of the functional unit of filtration the nephron. Greater functionality as measured by standard techniques such as inulin clearance may thus be achieved.

A feature of kidney formation from a transplanted metanephros is that the metanephros is a bundle of cells which develops into a mature, functional organ. The

5 teachings from prior art disclosures related to transplantation of cells which are already functional, for example the pancreatic cells in USP5,629,194 (Dinsmore), are thus not directly transferable to development of transplanted metanephroi.

10 The large blood vessel may be a branch of the aorta. For example, the large blood vessel may be a renal artery, an iliac artery or an hepatic artery.

Alternatively, the large blood vessel may be a branch of the vena cava. For example, the large blood vessel may be a renal vein, an iliac vein or an hepatic vein.

15 In a further embodiment of the invention, the method comprises the steps of making a surface abrasion on a superior lobe of a liver of the recipient and implanting the metanephros on the abrasion to allow the metanephros to connect to an hepatic blood supply. The Experimental
20 section below shows evidence for improved development of metanephroi thus implanted.

In another embodiment, the metanephros has an intact renal capsule.

25 In a preferred embodiment of the invention, at least two whole metanephroi, each with renal capsules intact, are implanted into the recipient.

30 The metanephros may be allogeneic to the recipient. Alternatively, the metanephros may be xenogeneic to the recipient.

35 The method may further comprise immunosuppressing the recipient.

The metanephros may be obtained from the donor within a certain stage after embryonic development of the metanephros begins. For example, the metanephros may be obtained from the donor within 2 to 4 days after embryonic development of the metanephros begins. Table 1 shows the time-course in days of metanephros development and gestational period in some vertebrates.

Table 1

10

	<u>Metanephros</u> <u>Formation (days)</u>	<u>Gestational</u> <u>Period (days)</u>
	Human	267
15	Macaque	167
	Pig	114
	Guinea Pig	67
	Rabbit	32
	Rat	22
20	Mouse	19
	Hamster	16
	Chick	21

25 The metanephros may be obtained from the donor prior to the presence of blood vessels within the metanephros.

The recipient may have reduced functional renal mass prior to implantation of the metanephros.

30

In a further embodiment, after the ureter of the chimeric kidney develops, a ureter to ureter anastomosis may be performed to provide fluid communication between the ureter of the chimeric kidney and a ureter of the recipient.

35

In another embodiment, after the ureter of the chimeric kidney develops, a ureter to bladder anastomosis is performed to provide fluid communication between the ureter of the chimeric kidney and the bladder of the recipient. In this embodiment, the metanephros is implanted preferably on or near the iliac vein or iliac artery.

The mammalian recipient may be a juvenile or adult.

The metanephros may be implanted within five hours, preferably 2 to 4 hours, after removal from the embryonic donor.

Prior to implantation of the metanephros, renal tissue may be removed from the mammalian recipient.

In a further aspect of the invention, there is provided a method of growing a donor embryonic mammalian metanephros in a mammalian recipient, comprising the step of implanting the metanephros on or near a large blood vessel of the recipient under conditions that allow the metanephros to become vascularised.

In another aspect of the invention, there is provided a method of reducing the inflammatory response following implantation of a donor embryonic mammalian metanephros in a mammalian recipient, comprising the step of implanting the metanephros on or near a large blood vessel of the recipient under conditions that allow the metanephros to become vascularised.

The invention encompasses transplantation of metanephroi under the membrane covering the aorta in rats or other mammals or under the membrane covering either the renal or femoral artery in large mammals. This would allow the

transplants to develop a blood supply from high pressure arterial sources.

5 The method of the invention may be extended to the formation of other chimeric organs which requires good vasculature and appropriate rapid development.

10 Various embodiments of the invention will now be described by way of example with reference to the drawings, in which:

Fig. 1A,B are photographs showing differences in gross morphology between metanephroi transplanted onto either the omentum (A) or near the renal vein (B) 16 days post transplantation. Arrowheads show the blood vessel supplying the transplants;

20 Fig. 2A-C are micrographs showing (A) rudimentary structures of metanephroi transplanted from E15 embryos into a host; development of mature structures in transplants 16 days post-transplantation from the omentum (B) and near the renal vein (C). G= glomeruli; arrowheads denote nephron tubules;

25 Fig. 3A,B show lectin stained architecture of the collecting tubule system 35 days post-transplantation onto the omentum (A, top - photograph; bottom - micrograph) and near the renal vein (B, top - photograph; bottom - micrograph). G= glomeruli; and

30 Fig. 4A,B show surface abrasion of the liver results in omentum metanephroi transplants with an hepatic blood supply (photograph A, arrowhead denotes blood vessel); and the development of mature kidney structures within 12 days of transplantation (micrograph B) including glomeruli (G),

35

collecting tubules (CT), blood vessels (BV) and nephron tubules (arrowheads).

Experimental

Locations within the peritoneal cavity have been investigated as sites for metanephroi transplantation. In each case the metanephroi were transplanted close to a substantial blood source in the hope they would derive their vasculature from a major vessel.

10 Example 1: Transplantation of metanephroi to the Renal Vein

15 Materials & Methods

Extraction of metanephroi

A growth factor cocktail was prepared at the following concentrations: Human recombinant IGF-I $10^{-7}M$ (Upstate Biotech #01-208) Human recombinant IGF-II $10^{-7}M$ (Upstate Biotech #01-142), Human recombinant TGF α $10^{-8}M$ (Upstate Biotech #01-165), Human recombinant HGF $10^{-8}M$ (R&D systems Ltd. #294-HGN-005), Human recombinant VEGF $10^{-7}M$ (Upstate Biotech #01-185), Human recombinant FGF 5 μ g/ml (R&D systems #234-FSE-025), Human recombinant NGF-I 5 μ g/ml (R&D systems #256-GF-100), Retinoic acid $10^{-6}M$ (#R2625), Corticotropin releasing factor 1 μ g/ml (Sigma #C3042), Iron saturated transferrin 5 μ g/ml (Sigma #T8158)

Embryonic day 15 metanephroi were extracted from time-mated Sprague-Dawley rat embryo's using a dissecting microscope. Only metanephroi that contained a reasonable length (approximate minimum of 0.1mm) of ureter were selected for transplantation. The metanephroi to be transplanted were placed in the growth factor cocktail outlined above, for between 2 to 5 hours on ice prior to transplantation.

Surgery

A 250g female Sprague-Dawley rat was anaesthetised by intra-peritoneal or intra-muscular injection of ketamine and xylozine. Once sufficient anaesthesia was achieved the rat was immobilised on a rodent surgery board and the abdomen was shaved and washed with anti-microbial agent. A 4-6 cm laporotomy was performed with the incision held open using retractors. The native renal mass (left kidney) was exposed by displacing the digestive system (large and small intestines as well as the other viscera) and covering them with moist gauze to prevent dessication of the tissue. A pouch was created in the tissue close to the renal vein near the junction with spermatic vein using forceps and a single metanephroi (incubated in growth factors) was placed into the pouch, which was then closed using a non-absorbable 8/0 cromatic cat gut suture (ethicon). The digestive system was carefully put back in place and the laporotomy was closed in two layers.

20 Analysis of metanephroi

16 days later the rat was euthanised by dislocation of the neck, the laporotomy was re-opened and the transplanted metanephroi identified and removed for analysis.

25 Renal histology

Tissue samples were fixed in 2% paraformaldehyde overnight at 4°C, then dehydrated and embedded in paraffin. Five micrometer sections were cut and mounted and stained with Harris's haematoxylin and eosin prior to being viewed by light microscopy.

Lectin staining (Dolichos biflorus (DB) lectin)

35 Tissues were fixed in 2% paraformaldehyde for 30 minutes at 4°C, permeabilised with 0.1% saponin and then incubated with FITC-conjugated DB (50µg/ml, Vector Labs.) in a

humidified chamber for 60 minutes at 37°C. After extensive washing, tissues were post-fixed in 2% paraformaldehyde again for 5 minutes and viewed by standard immunofluorescence microscopy. The specificity of DB lectin has been demonstrated previously (Laitinen L et al., 1987, J. Histochem. Cytochem.).

Inulin Clearance

The function of the transplanted kidneys can be assessed by standard techniques such as inulin clearance.

Results

Metanephroi transplantation near the renal vein can result in the transplants deriving a blood supply from either the renal vein or spermatic vein both of which carry large volumes of blood. Transplants growing near the renal blood supply appear to have a better gross morphology i.e. they more closely resemble the native kidney in terms of shape and colour compared to samples transplanted onto the omentum as shown in Fig. 1.

Light microscopy reveals that samples grown on the omentum and near the renal vein both develop mature glomeruli and undergo tubulogenesis to form the distal and convoluted tubules of the mature nephron within 12 to 16 days post-transplantation (see Fig. 2).

However, the transplants near the renal vein develop with more tubules and more glomeruli. Moreover, these glomeruli are larger in size.

Lectin staining reveals the superior collecting duct system of the chimeric kidneys derived from metanephroi transplanted near the renal vein compared with those transplanted near the omentum.

Fig. 3 shows lectin staining to show the architecture of the collecting tubule system 35 days post-transplantation that transplants onto the omentum develops a sparse collecting system with no defined symmetry (Fig. 3A top), further more, histologically the transplants onto the omentum have large areas of inflammation and lack either defined glomeruli or tubules (Fig. 3A bottom). By comparison the transplants near the renal vein have a well-developed collecting system which displays both symmetry and the presence of adult structures such as the kidney medulla (Fig. 3B top). Histologically these transplants have mature glomeruli which are extremely abundant (Fig. 3B bottom). One would expect therefore that metanephroi transplanted near to the renal vein would develop into more functional chimeric kidneys than those transplanted to the omentum.

Discussion

Advantages of this new site of transplantation include:

- Improved blood pressure supply to the transplants which may improve function
- Improved location close to native renal tissue, which may improve further procedures such as anastomosis of ureters.
- Improved development of transplants in the absence of either unilateral or 5/6 contralateral nephrectomy.
- Reduced inflammation and/or immune response.

The amount of function Hammerman has observed when transplanting metanephroi into adult hosts may not entirely be related to their innate functional ability. For example, the low renal function (5-7%) of the metanephroi may be related to the blood flow into the omentum. It is currently thought that higher blood pressure provided at the sites mentioned in the present

invention may improve chimeric kidney function.

The reduction in inflammatory and/or immune response which is clear in above data for the transplant of metanephroi near the renal vein compared with controls of the omentum is highly counter-intuitive. One would expect that there would be a greater number of white blood cells able to enter the graft when transplanted into a site which will be better vascularised.

Example 2: Surface Abrasion of Liver

A novel alternative method for increasing blood flow to metanephroi is to create a surface abrasion on the superior lobe (right lobe) of the liver. This results in vasculature outgrowth from the liver to the metanephroi and allows the transplant to connect to the hepatic blood supply (Fig. 4A). Histologically these transplants have developed mature structures within 12 days of transplantation (Fig. 4B).

Example 3: Alternative surgical locations

An alternative location for metanephroi transplantation is close to the iliac blood supply. This is the site of choice for current human whole organ kidney transplants due to the blood volume and pressure of this system. Furthermore, transplantation of metanephroi into this region would allow anastomosis of the transplant ureter to the host bladder using an antirefluxing extravesical ureteroneocystostomy to prevent reflux of urine from the bladder into the metanephroi transplant. Preliminary experiments have shown that metanephroi transplanted into this region develop extremely well.

Claims

1. A method of increasing the nephron mass of a mammalian recipient comprising implanting a metanephros of an embryonic mammalian donor on or near a large blood vessel of the recipient under conditions that allow the metanephros to become vascularised.
2. The method according to claim 2, wherein the vascularised metanephros forms a chimeric kidney that produces urine and develops a ureter that facilitates externalisation of the urine.
3. The method according to either of claim 1 or claim 2, in which the large blood vessel is a branch of the aorta.
4. The method according to claim 3, in which the large blood vessel is a renal artery, an iliac artery or an hepatic artery.
5. The method according to either of claim 1 or claim 2 in which the large blood vessel is a branch of the vena cava.
6. The method according to claim 5; in which the large blood vessel is a renal vein, an iliac vein or an hepatic vein.
7. The method according to either of claim 1 or claim 2, comprising the steps of making a surface abrasion on a superior lobe of a liver of the recipient and implanting the metanephros on the abrasion to allow the metanephros to connect to an hepatic blood supply.
8. The method according to any preceding claim, in which the metanephros has an intact renal capsule.

9. The method according to any preceding claim, in which at least two whole metanephroi, each with renal capsules intact, are implanted into the recipient.

5

10. The method according to any preceding claim, in which the metanephros is allogeneic to the recipient.

10

11. The method according to any of claim 1 to 9, in which the metanephros is xenogeneic to the recipient.

12. The method according to any preceding claim, further comprising immunosuppressing the recipient.

15

13. The method according to any preceding claim, in which the metanephros is obtained from the donor within 2 to 4 days after embryonic development of the metanephros begins.

20

14. The method according to any preceding claim, in which the metanephros is obtained from the donor prior to the presence of blood vessels within the metanephros.

25

15. The method according to any preceding claim, in which the recipient has reduced functional renal mass prior to implantation of the metanephros.

30

16. The method according to any of claims 2 to 15, in which after the ureter of the chimeric kidney develops, a ureter to ureter anastomosis is performed to provide fluid communication between the ureter of the chimeric kidney and a ureter of the recipient.

35

17. The method according to any of claims 2 to 15, in which after the ureter of the chimeric kidney develops, a ureter to bladder anastomosis is performed to provide

fluid communication between the ureter of the chimeric kidney and the bladder of the recipient.

18. The method according to claim 17, wherein the metanephros is implanted on or near the iliac vein or iliac artery.

19. The method according to any preceding claim, in which the mammalian recipient is a juvenile or adult.

20. The method according to any preceding claim, in which the metanephros is implanted within five hours, preferably 2 to 4 hours, after removal from the embryonic donor.

21. The method according to any preceding claim, in which prior to implantation of the metanephros, renal tissue is removed from the mammalian recipient.

22. A method of growing a donor embryonic mammalian metanephros in a mammalian recipient, comprising the step of implanting the metanephros on or near a large blood vessel of the recipient under conditions that allow the metanephros to become vascularised.

23. A method of reducing the inflammatory response following implantation of a donor embryonic mammalian metanephros in a mammalian recipient, comprising the step of implanting the metanephros on or near a large blood vessel of the recipient under conditions that allow the metanephros to become vascularised.

1/8

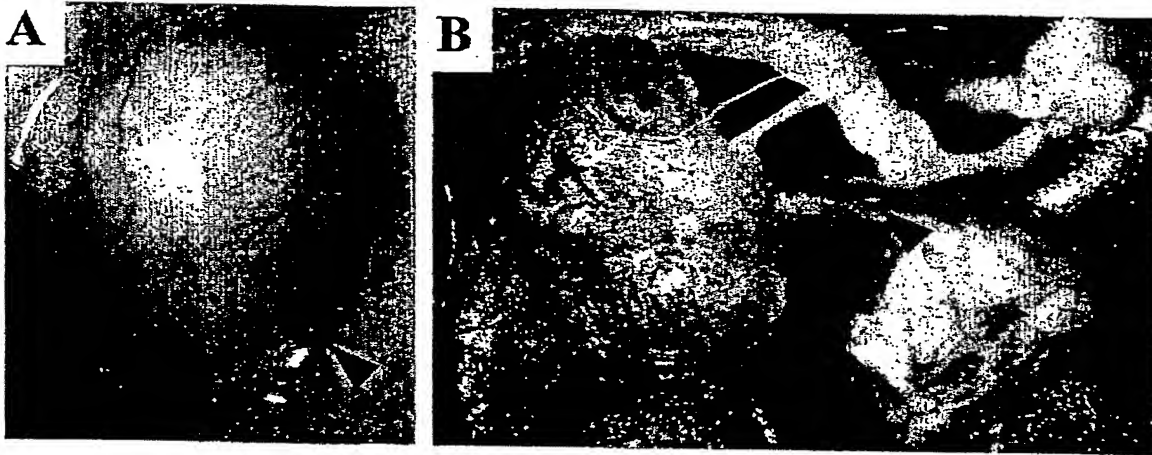


Figure 1

Figure 2A



Figure 2B

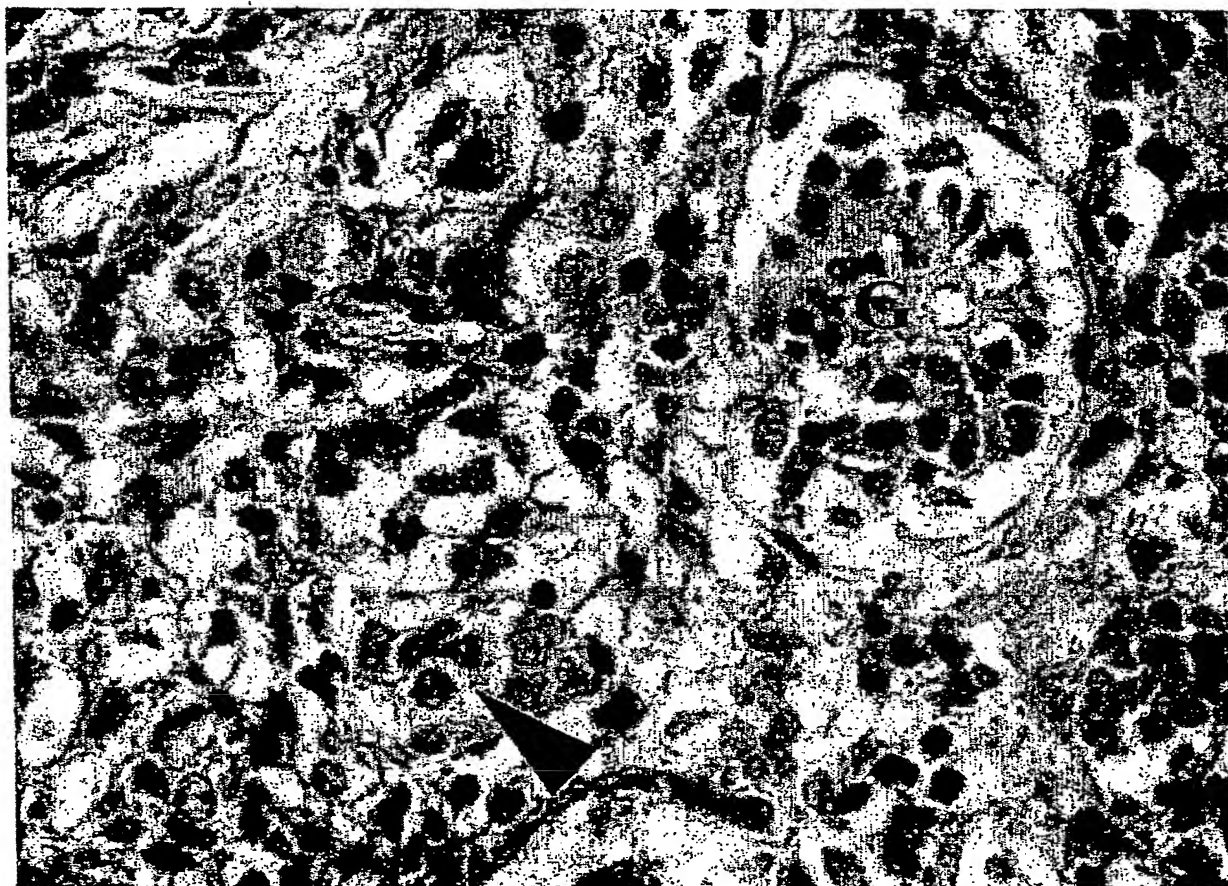
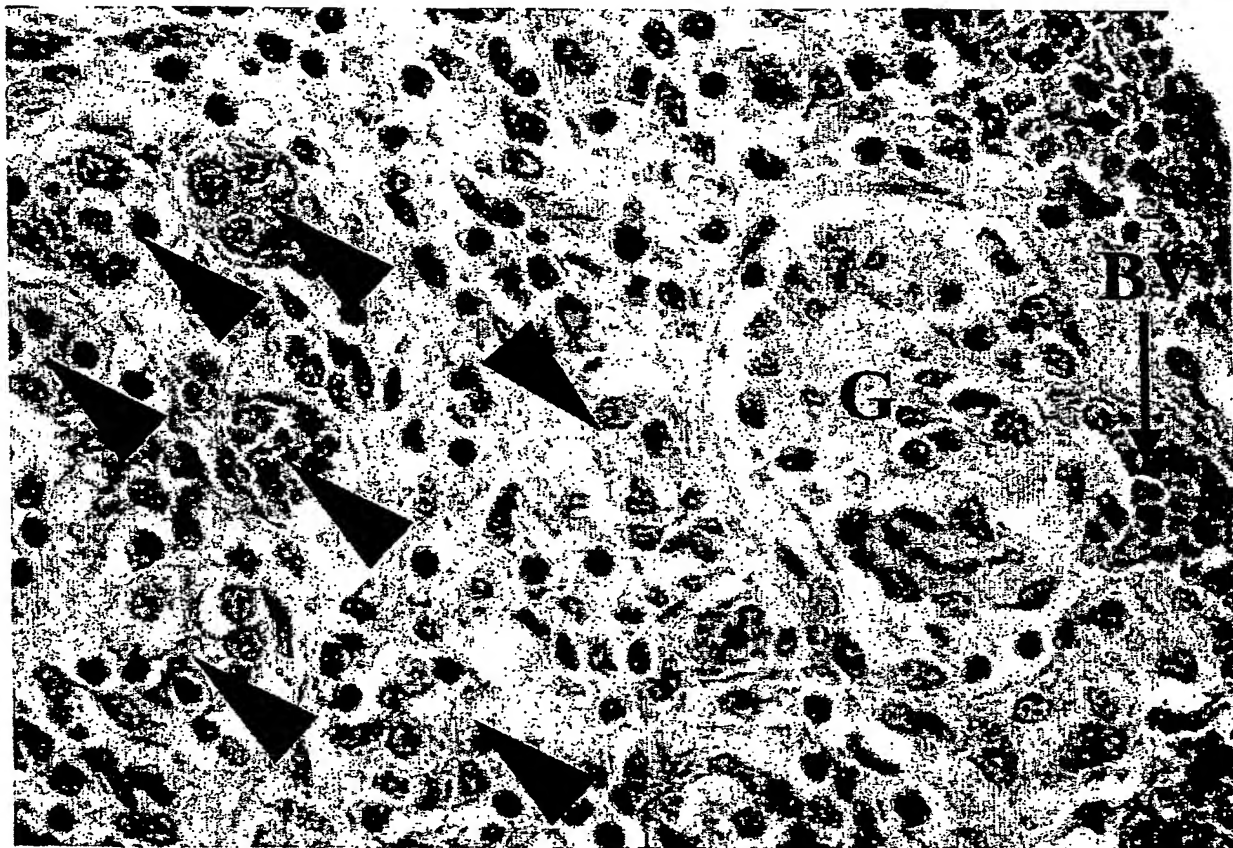
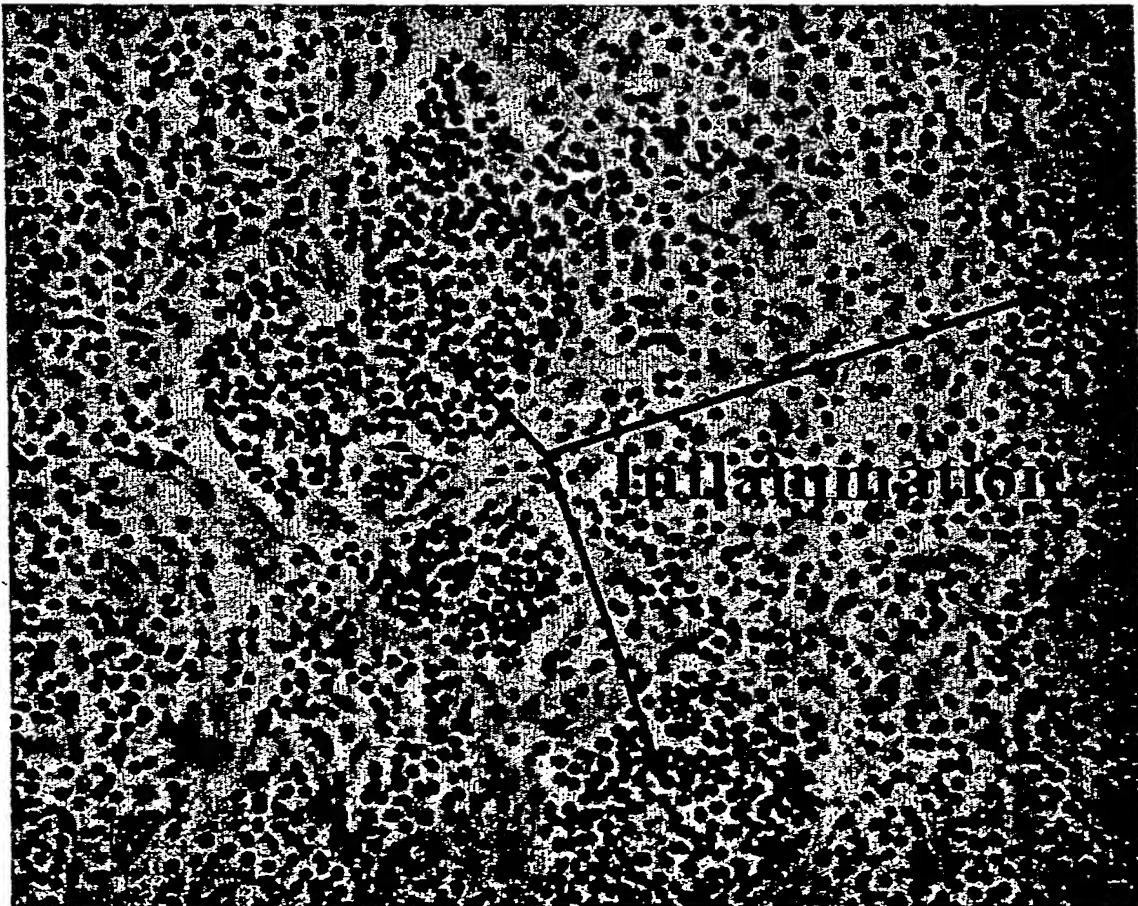
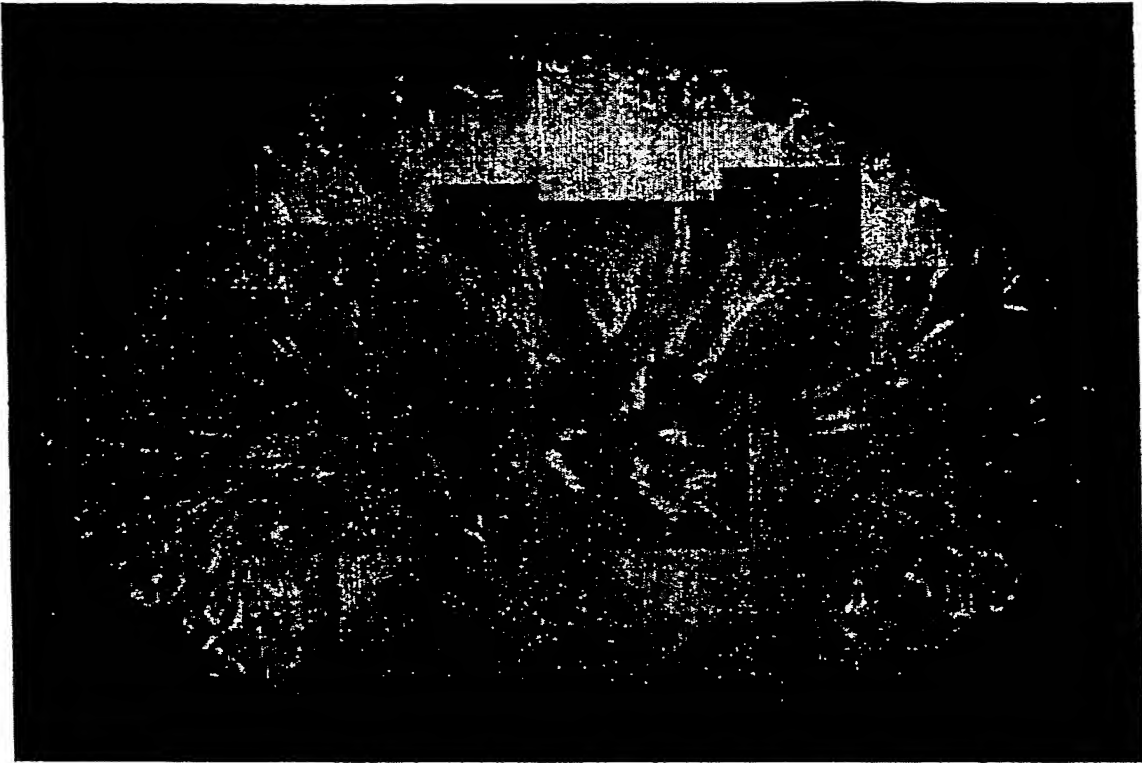


Figure 2C



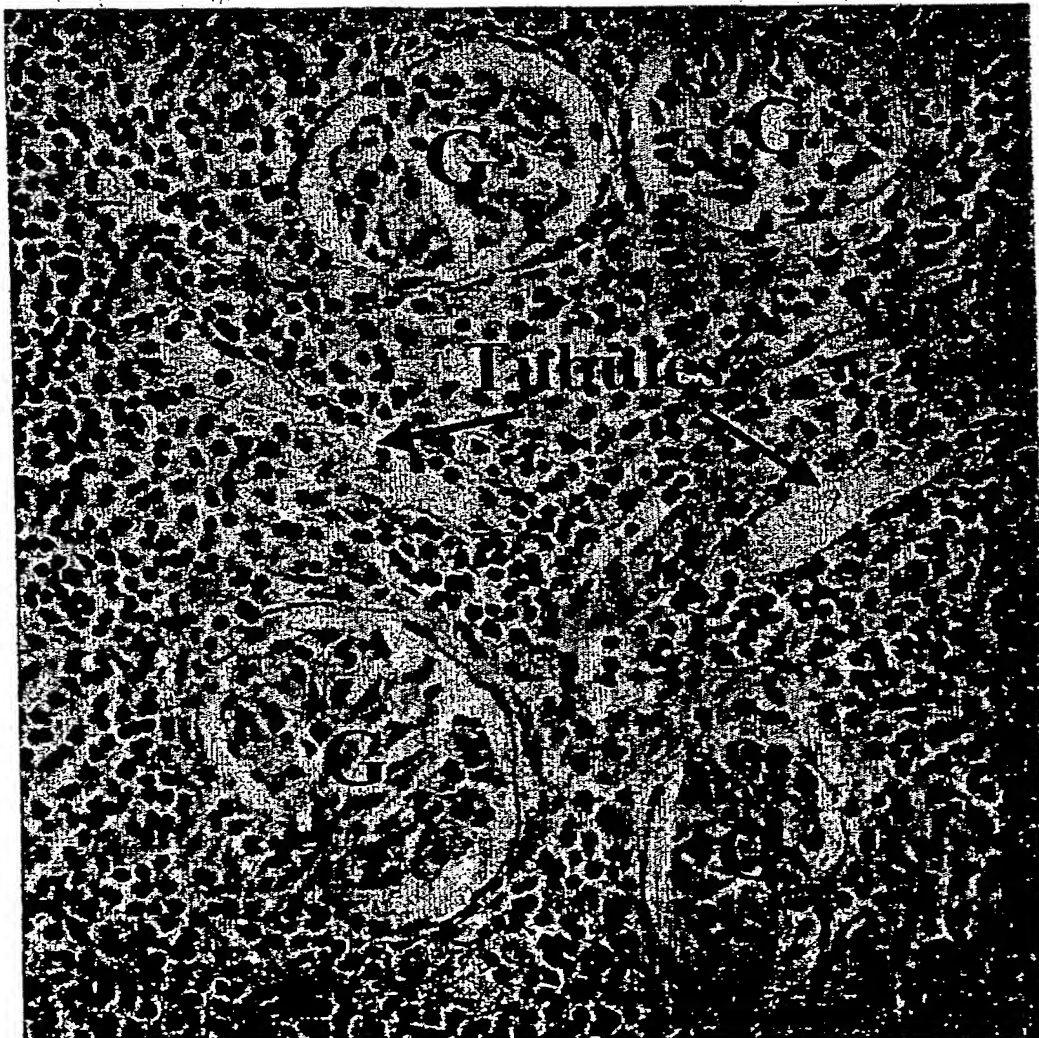
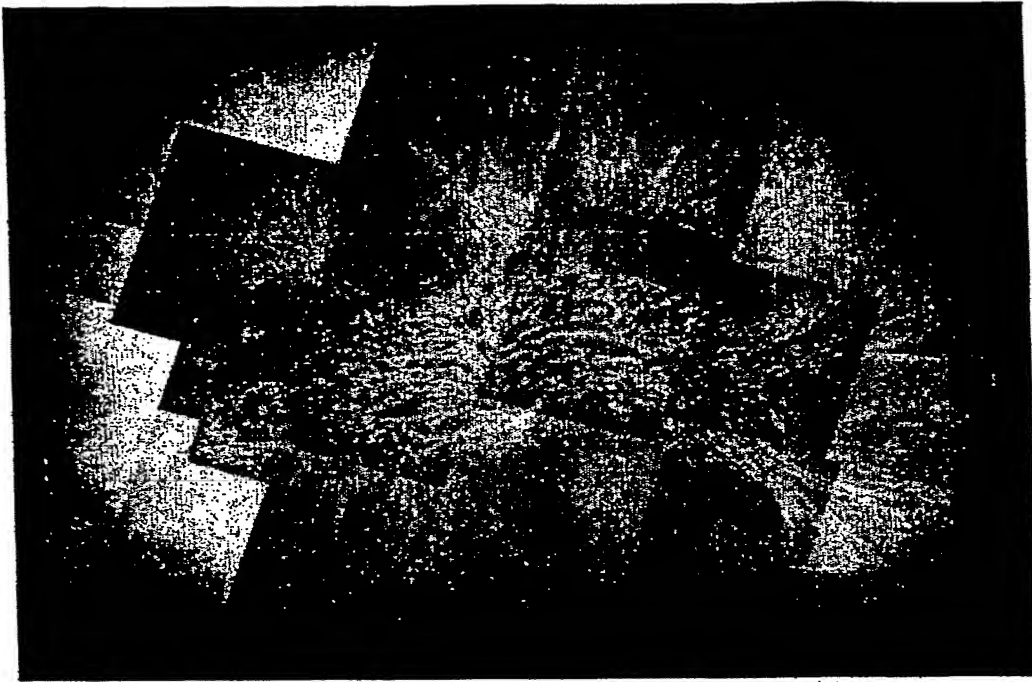
5/8

Figure 3A



6/8

Figure 3B



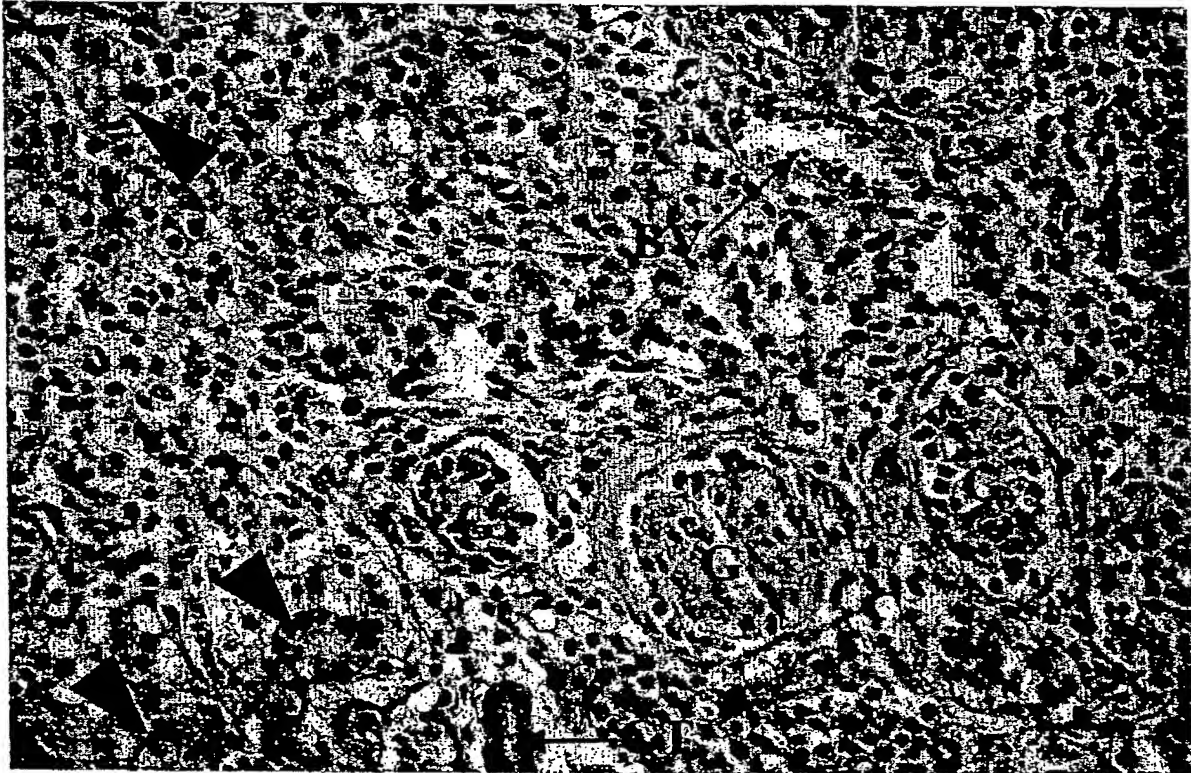
7
8

Figure 4A

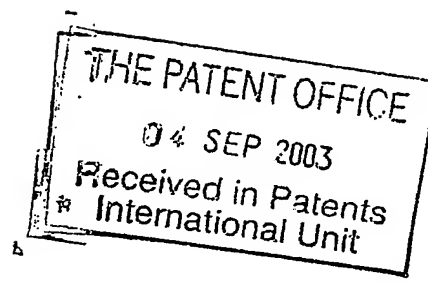
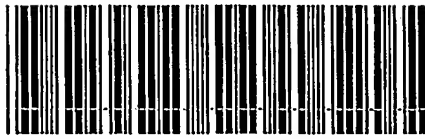


8/8

Figure 4B



PCT Application
GB0303575



**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record.**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.